November 16, 1956

Mr. J. Lein
Bristol Labs.
Syracuse 1, N.Y.

Dear Joe:

We have run into a very curious effect of penicillin in our L-form studies. When plated into a peptone-meat-extract-sucrose medium, K-12 will give a high yield ofLcolonies, but only if rather large amounts of penicillin are added, 1000-10.000 u/ml. However, 100 u/ml are sufficient to strip the walls. Therefore at this level of penicillin, there is no growth at all, either bacillary or L (protoplastic). To put it differently, penicillin seems to be a growth factor for the proliferation of protoplasts, in addition to its effect in inducing them at lower concentrations.

This is a serious question in our attempts to find wall-defect mutants in which wall-formation is blocked genetically instead of by an inhibitor. We are wondering whether penicillin itself is the growth factor, possibly acting by a secondary inhibition of some other reaction, or whether the growth factor is some contaminant or degradation product of the penicillin. We might be able to settle this question, and know how to proceed further if we could repeat the experiment with penicillin preparations more highly purified than the commercial material (penicillin sodium [redacted] Sharp&Dohme) we now get via the hospital. Can you help me on this? We would need 100mg - 1 g. for the experiment; if we get the same effect as before, we will conclude that the growth factor is not a contaminant, though it might still be a degradation product. (However, we already know that penicillin heated at neutral pH has lost its "growth-factor" activity.) I'll send you a picture of a gradient plate sometime that looks like this:

Any news on "anti-dap" and the like? I have to tell you that probably more than a few other people are on to the general idea:e.g., I have an ms. from Park & Strominger (for Science) which discusses penicillin in relation to uridine-diphospho-R-hexosamine. [this being the carboxy-ethyl-3-glucosamine]: "competitive inhibitors related to the several unique structures of the wall and the nucleotide might now be devised which would be useful as chemotherapeutic agents." But no mention anywhere of DAP as a specific target—so far.

One final bit of intelligence: Lilly's has evidently awoken to genetics, anyhow theyve offered Tom Nelson a job in the development division, which he is debating taking. For our part, I can only hope this enlightenment will spread even further.

Sincerely,

Joshua Lederberg